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Dietary therapies for childhood epilepsy

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Summary
Ketogenic diet composed of high fat and low carbonhydrate was introduced as a therapeutic alternative for epilepsy in early 20's. As new antiepileptic agents such as phenytoin were discovered, the popularity of the diet waned until 90's. Studies on efficacy of diet in refractory epilepsy reported that approximately half of the children had a significant reduction 15% of whom were seizure free. With growing body of evidence and introduction of diet modifications, ketogenic diet was promoted as a first line treatment for epileptic encephalopathies such as myoclonic-astatic epilepsy, Dravet syndrome and infantile spasm. *(Turk Arch Ped 2013; 48: 275-280)*

Key words: Dravet syndrome, epilepsy, infantile spasm, ketogenic diet, myoclonic astatic epilepsy

Introduction

Currently, seizures of most epilepsy patients can be controlled with anticonvulsant drug treatment, while resistant seizures of some patients direct physicians to search for other treatment methods. The relation of this kind of resistant epilepsies with nutrition has been known for long years. In the beginning of the 1900's, investigators drew attention to the fact that epileptic seizures could be stopped by complete fasting (1,2). However, naturally complete fasting is not a sustainable treatment method. Therefore, a diet which mimiced acidosis, fluid loss and ketosis which occur in the fasting state and which could be used for years was developed by Dr. Wilder (3) in 1921 in Mayo Clinic. This treatment which is called ketogenic diet (CD) has been used in treatment of epilepsy for more than 100 years without a change in its content. With release of phenytoin in 1938 drug therapies came to the forefront and use of CD decreased in the following years. In the second half of the 20th century, a few centers in which diet therapy was being used remained and most neurologists regarded diet therapies as "alternative" or "complementary" medicine. However, inititation of CD in 1994 in a 2 year-old epileptic boy in whom multiple drugs and surgical treatment were unsuccessful with the intervention of the family and improvement of seizures completely (4) once again increased the attention of physicians and families related with diet therapies. In the last 20 years, hundreds of publications have been added to the medical literature, international symposiums have been arranged and consensus reports have been published (5,6). In this article, ketogenic diet and other diet methods in treatment of childhood epilepsies will be discussed because of their current significance.

What is ketogenic diet?

Ketogenic diet is a nutritional regime containing high fat, low protein and low carbonhydrate and its calorie and total fluid content is limited to meet 80% of daily requirement. The ketogenic ratio (KR) is calculated as the ratio of fat contained in the diet to the sum of protein and carbonhydrate and it is 4:1 for a typical CD (5). A higher ketogenic ratio means more ketosis. In patients in whom protein requirement is high or diet cannot be applied

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appropriately because of side effects including infants and adolescents, lower ratios including 3:1 or 2:1 can be used (7). In a diet with a ketogenic ratio of 4:1, 90% of the daily calorie is provided by fat, 7% is provided by protein and 3% is provided by carbonhydrates (8). The most common sources of fat include butter, cream, oil and mayonnaise.

Ketogenic diet lists should be prepared individually for each patient. Keeping a three-day diet record of the patient is recommended in terms of determining food preferences and preparing a diet list compatible with the palatal delight. The aim should be to give enough calorie such as to follow up the patient's own growth curve while arranging nutrition. Fluid restriction during ketogenic diet is controversial. Since a marked efficiency of fluid restriction has not been demonstrated in stopping seizure activity, it is no longer used in most centers (8,9). Since it is observed that most epilepsy patients receive not even 80% of daily fluid requirement before CD when diet records are kept, the term limitation is not accurate (10). It is recommended that 100% of daily fluid should be given to patients who are immobile, who have a history of nephrolithiasis and who use carbonic anhydrase inhibitor (topiramate, asetazolamide, zonisamide) (11).

In the begining of the treatment method, it is recommended that patients should be followed up by hospitalization, because patients will enter a 24-48-hour fasting period in the beginning of CD. During the fasting period, blood glucose levels should be measured every 4-6 hours and urinary ketone should be tested daily (8). At the time of hospitalization and in the following days, serum electrolytes, urea, creatinine should be measured daily. The patient should be weighed every morning and his/her input/output fluid should be recorded. The diet should be arranged such as to complete urinary ketone at the moderate-high level (80-160 mg/dL) (9). Nutrition is opened gradually in three days following fasting, the highest level is reached and the patient can be discharged. The problems which can be encountered during the fasting period include transient hypoglycemia, vomiting, constipation and mild acidosis and these conditions can be easily intervened in the hospital setting. Some authors have reported that equal efficiency occurs in seizure control without fasting period, but fasting is still applied in most centers, since it is thought the effect starts faster with fasting (12).

Ketogenic diet is a type of diet which has an unpleasent taste because of its high fat content and which can be compansated with difficulty (6). Therefore, other diet therapies which are more appropriate for palatal delight and which have a higher carbonhydrate and protein content compared to CD have been developed. Currently, there are three more diet therapies other than classical CD which have been proved to be efficient in treatment of epilepsy and which are being used: medium chain triglyceride (MCT) diet, modified Atkins diet (MAD) and low glycemic index therapy (LGIT). In these therapies, the protein and calorie rates received by patients are higher, they can be compensated better and limit weight gain and growth with a lower rate (Table 1). In addition, the patient does no need to be hospitalized to initiate the diet, since fasting is not required in advance (13,14).

Since medium chain fatty acids produce more ketone per unit energy (15), patients who use MCT diet can consume less fat and more protein and carbonhydrate compared to CD. Thus, food options become richer. However, compliance is low, since foods should be weighed and measured and time should be spent during preparation of meals (16). In low glycemic index therapy, only foods with a glycemic index below 50 are allowed. Although this type of diet containes a richer food spectrum and more protein, approximately 1/4 of patients have found this diet excessively limiting (17).

In MAD which was started to be used by Kossoff and his team in 2003 in Johns Hopkins Institute for the first time, there is no calorie, fluid or protein limitation (13). In this diet, carbonhydrates are limited up to 10 g/day and high fat intake is supported to provide ketosis. In MAD which is

Table 1. Comparison of four different diet types for nutrition containing 1500 kcal daily

Diet	Fat (g), % clorie	Protein (g), % calorie	Carbonhydrate(g), % calorie
Classical ketogenic diet			
4:1	150 (%90)	25.5 (%7)	12 (%3)
3:1	144	27	21
2:1	138	30	39
1:1	115	55	60
OMedium chain triglyceride diet	117 (%70)	37.5 (%10)	75 (%20)
Low glycemic index therapy	100 (%60)	100 (%27)	50 (40-60) (%13)
Modified Atkins diet	117 (%70)	94 (%25)	19 (%5)

*Values are calculated approximately.

preferred by many centers currently, ketone production is variable and its efficiency has been shown to be increased with supportive high-fat formulas in the first month of treatment (18). It is recommended that the diet most appropriate for the patient's compliance should be selected in accordance with the patient's individual properties and the views of families and dietician, because it is impossible to continue the efficiency of treatment if close monitoring is not provided (16).

The place of ketogenic diet in treatment of epilepsy

It has been reported that ketogenic diet may be useful in many seizure types and resistant epilepsy. The limits of diet indications which were previosuly defined for cases unresponsive to at least two anticonvulsant drugs with frequent seizures and not appropriate for epilepsy surgery become more clear with the study of the International Ketogenic Diet group published in 2009 (5). Two special conditions in which ketogenic diet can be used as the first-line therapy have been defined: Glucose transporter type 1 deficiency and piruvate dehydrogenase deficiency. In glucose transporter type 1 deficiency, glucose transportation in the blood-brain barrier is disrupted; microcephaly, resistant seizures and movement disorders occur in the patients (19). In piruvate kinase deficiency, piruvate cannot be transformed to acetyl-coenzyme A and a neurodegenerative picture accompanied by seizures occcurs (20). With ketogenic diet ketone (asetoacetate, beta hydroxy butirate) is provided to the brain as optional fuel instead of these metabolic pathways.

Recent reports about the efficiency of MAD and LGIT which can be applied more easily compared to classical CD in epileptic patients suggest that diet therapy can be applied earlier in epilepsy (13,14). Considering the extensiveness and ease of use of ketogenic formula, it is expected that diet treatment will be used extensively in infants with infantile spasm in the forthcoming period. Hong et al. (21) reported that the seizure frequency decreased by more than 50% in 64% of 1104 patients with infantile spasm in a diet period of 6 months and 34% of the patients remeained seizure-free in the study they published in 2010. The authors emphasized that diet treatment could be considered just after failure of adrenocorticotropic hormone and vigabatrin treatment.

It has been reported that ketogenic diet is superior to new anticonvulsant drugs in patients with myoclonic astatic epilepsy which is one of the myoclonic epilepsies of genetic origin (22). In patients with Dravet syndrome which is another form of this epilepsy group, Nabbout et al. (23) found that diet decreased attention deficit in 56% and impulsivity and nervousness in 28% in addition to seizure control. Although especially vigabatrin has been shown to be effective in seizures related with tuberosclerosis, different centers have reported that ketogenic diet might be an efficient alternative method together with surgical treatment even in focal seizures (24,25).

Conditions for which the efficiency of diet is being reported are increasing gradually in the form of case reports or series. The efficiency of diet has been reported in seizures related with Rett syndrome, Lafora body disease, Landau Kleffner syndrome which is known as epileptic aphasia and neuronal seroid lipofuscinosis which is a lysosomal storage disease (26). Fever induced refractory epileptic encephalopathy (FIRES) is a picture of encephalopathy described in previously healthy children. In these patients, no specific infectious agent can be found and a refractory status picture is typical. Probably, the most amazing results about classical ketogenic diet included small case series in which status epilepticus was reported to be terminated in these patients (27,28).

The mechanism of action of ketogenic diet

Investigators usually have to develop methods in the opposite direction to elucidate the mechanism of action of ketogenic diet; understanding the reason of a method which is known to be effective instead of searching for treatment for a disease of which the pathophysiology is known. Increasing investigations indicate multiple variables working synergistically instead of a single mechanism of action (29).

In early animal studies, the convulsion-preventing effects of administration of intraperitoneal asetoacetate had been shown in different experimental models (30,31). In Mouse models of Dravet syndrome, a relation was found between high beta-hydroxybutirate levels and seizure control (32). In addition to investigators (33) who have reported that ketogenic diet with a higher ketogenic ratio (6:1) are more efficient, there are many studies in which seizure triggering has been shown to be prevented after ketosis (34,35,36). With ketogenic diet the number and affinity of GAMA receptors increase and the synthesis of endogenous glutamate antagonists is induced (37,38). Studies based on the assumption that multiple unsaturated fatty acids can equilibrate neuronal cell have yielded contradictory results (39,40). Ketogenic diet has been shown to protect hippocampal cells from glutamate-mediated excitation damage and its neuroinflammatory protector property has been emphasized (41). Ketones protect the brain from free oxygen damage by decreasing cerebral coenzyme Q10 semiquinone levels and stimulating hippocampal glutation peroxidase (42,43). In addition, it has been shown that diet increases neuronal high-energy molecular densities (44).

Recently, the effect of ketogenic diet on carbonhydrate metabolism and leptin levels has drawn the attention of investigators. High fat intake and limited carbonhydrate inhibit the glycolysis pathway. Glucose analog 2-deoxy

D-glucose which inhibits the glycolysis pathway show marked anticonvulsive effect acutely and chronically (45). Acute action has been associated with inhibition of postsynaptic currents and chronic action has been associated with regulation of the brain-derived neurotrophic factor (BDNF) gene (46,47). It is thought that increased leptin levels with diet are involved in the effect of anticonvulsive effect of ketogenic diet. Increased leptin levels decrease the frequency and time of seizures by inhibiting AMPA-related excitation (48).

Contraindications of ketogenic diet

In some metabolic diseases, application of CD is contraindicated; these include piruvate carboxylase deficiency, primary carnitine deficiency, fatty acid oxidation disorders (including carnitine transporter disorders) and porphyria (16). Therefore, patients with refractory epilepsy selected for CD should be screened in terms of these diseases before diet (Table 2).

Relative contraindications include nephrolithiasis, hypercholesterolemia, combined use with phenobarbital and severe gastroesophageal reflux (8,16)

Side effects of ketogenic diet

Independent of the diet type, CD treatment is a significant therapy method with potential side effects (49). Therefore, families should be informed about the fact that CD is not a "natural" or "complementary" treatment method before starting this diet.

Table 2. Tests to be ordered and follow-up chart in ketogenic diet

Before starting	
Physical examination	Definition of daily calorie requirement according to age, height, body weight and level of mobility
Blood	Fasting lipid profile, urea, creatinine and electrolytes, urgent carnitine, lactate
Urine	Measurement of pH and density, Ca/Cr ratio, organic acid
Follow-up	
Physical examination (every three months)	Evaluation of growth by measurement of height, weight
Blood (every 3-6 months)	Complete blood count, calcium, phosphorous, magnesium, alkaline phosphatase, fasting lipid profile, albumin, lipase, hepatic transaminases, anticonvulsant drug levels, 25-hydroxy vitamin D, carnitine, beta-hydroxy butirate
Urine	Complete urinalysis, Ca/Cr ratio
Cardiological evaluation (yearly)	Echocardiogram

In addition to transient side effects observed in the fasting period, renal stones, dislipidemia and pause in growth may be observed in 5% of the patients (50,51,52). None of these side effects necessitate discontinuation of treatment. However, intolerance related with gastrointestinal side effects (vomiting, loss of appetite, constipation, felux) and discontinuation of diet is observed especially in adults (53). Since albumin and carnitine levels of the patients may decrease, measurement of blood levels is useful. Although carnitine support is controversial, it is recommended only in patients who feel weak despite intake of sufficient calorie (54). Specific vitamin deficiency or mineral deficiency including selenium and progressive loss of bone mineral compound may be observed (55). Very rarely, cases of cardiomyopathy related with association of acidosis and selenium deficiency (56) and fatal pancreatitis related with hyperlipidemia (57) have been reported.

Follow-up and prevention of complications

Patients who receive ketogenic diet should be followed up in special centers by a team composed of physicians and dieticians. One mission of the ketogenic diet team is to prevent complications before they develop. Alternative diet therapies including modified Atkins diet or LGID or starting diet without fasting may be considered (12).

Before discharge from the hospital, families should have received diet education and learned to measure urinary ketone. In most centers, calcium, vitamin D, zinc and selenium supplements are prescribed to patients before discharge (58). Afterwards, evaluation of growth, nutrition and activity is recommended with 3-month intervals by outpatient follow-up (Table 2). At each clinical visit, fasting lipid levels, complete blood count and detailed metabolic examination should be ordered (5). Urinary calcium/creatinine ratio should be evaluated and oral alkalinization should be performed in patients with a high urinary calcium/creatinine ratio. Administration of oral citrate empirically with this objective (2 mEq/kg/day, in two doses) has been shown to decrease the frequency of nephrolithiasis from 6.9% to 0,9% (59). In patients with severe hyperlipidemia, KR may be reduced or switching to multiple unsaturated fatty acids may be applied (10). Cardiac evaluation by yearly echocardiogram should be kept in mind (16).

If ketogenic diet does not provide seizure control, diet is generally recommended to be discontinued after 3-6 months. In patients in whom diet is efficient, no decrease in seizure control has been reported when diet is discontinued after two years. However, diet therapy can be continued for a long time in children showing a normal growth-development in whom anticonvulsant drugs can be discontinued (10).

Conclusion

Ketogenic diet therapy is a convenient treatment option with confirmed efficiency in resistant childhood epilepsies. Currently, ketogenic diet has been included in the first-line therapies in selected patients. In our country, the number of centers where ketogenic diet is applied will increase as the awareness of physicians about ketogenic diet increases.

References

1. Guelpa G, Marie A. La lutte contre l'epilepsie par la desintoxication et par la re-education alimentaire. Revue de Therapie Medico-Chirurgide 1911; 78: 8-13.
2. Geyelin HR. Fasting as a method for treating epilepsy. Medical Record 1921; 99: 1037-1039.
3. Wilder RM. The effects of ketonemia on course of epilepsy. Mayo Clin Bulletin 1921; 2: 307-308.
4. Abrahams J. An introduction to the ketogenic diet: A treatment for pediatric epilepsy (videotape). The Charlie Foundation, Santa Monica, California 1994.
5. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, Buchhalter JR, Caraballo RH, Helen Cross J, Dahlin MG, Donner EJ, Klepper J, Jehle RS, Kim HD, Christiana Liu YM, Nation J, Nordli DR Jr, Pfeifer HH, Rho JM, Stafstrom CE, Thiele EA, Turner Z, Wirrell EC, Wheless JW, Veggiotti P, Vining EP; Charlie Foundation, Practice Committee of the Child Neurology Society; Practice Committee of the Child Neurology Society; International Ketogenic Diet Study Group. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia 2009; 50: 304-317.
6. Levy RG, Cooper PN, Giri P. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev 2012; 3: CD001903.
7. Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios--comparison of 3:1 with 4:1 diet. Epilepsia 2007; 48: 801-805.
8. Kossoff EH, Wang HS. Dietary therapies for epilepsy. Biomed J 2013; 36: 2-8.
9. Wirrell EC. Ketogenic ratio, calories, and fluids: do they matter? Epilepsia 2008; 49(Suppl 8): 17-19.
10. Turner Z, Kossoff EH. The ketogenic and Atkins diet: Recipes for seizure control. Practical Gastroenterology 2006; 30: 53.
11. Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EP. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. Epilepsia 2002; 43: 1168-1171.
12. Bergqvist AG, Schall JI, Gallagher PR, Cnaan A, Stallings VA. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. Epilepsia 2005; 46: 1810-1819.
13. Kossoff EH, Krauss GL, McGrogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy. Neurology 2003; 61: 1789-1791.
14. Pfeifer HH, Thiele EA. Low-glycemic-index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy. Neurology 2005; 65: 1810-1812.
15. Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology 1971; 21: 1097-1103.
16. Dhamija R, Eckert S, Wirrell E. Ketogenic diet. Can J Neurol Sci 2013; 40: 158-167.
17. Muzykewicz DA, Lyczkowski DA, Memon N, Conant KD, Pfeifer HH, Thiele EA. Efficacy, safety, and tolerability of the low glycemic index treatment in pediatric epilepsy. Epilepsia 2009; 50: 1118-1126.
18. Kossoff EH, Dorward JL, Turner Z, Pyzik PL. Prospective study of the modified atkins diet in combination with a ketogenic liquid supplement during the initial month. J Child Neurol 2011; 26: 147-151.
19. Klepper J, Leiendecker B. GLUT1 deficiency syndrome--2007 update. Dev Med Child Neurol 2007; 49: 707-716.
20. Wexler ID, Hemalatha SG, McConnell J, Buist NR, Dahl HH, Berry SA, Cederbaum SD, Patel MS, Kerr DS. Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations. Neurology 1997; 49: 1655-1661.
21. Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. Epilepsia 2010; 51: 1403-1407.
22. Kilaru S, Bergqvist AG. Current treatment of myoclonic astatic epilepsy: clinical experience at the Children's Hospital of Philadelphia. Epilepsia 2007; 48: 1703-1707.
23. Nabbout R, Copioli C, Chipaux M, Chemaly N, Desguerre I, Dulac O, Chiron C. Ketogenic Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: a prospective pilot study. Epilepsia 2011; 52: 54-57.
24. Kossoff EH, Thiele EA, Pfeifer HH, McGrogan JR, Freeman JM. Tuberous sclerosis complex and the ketogenic diet. Epilepsia 2005; 46: 1684-1686.
25. Coppola G, Klepper J, Ammendola E, Fiorillo M, della Corte R, Capano G, Pascotto A. The effects of the ketogenic diet in refractory partial seizures with reference to tuberous sclerosis. Eur J Paediatr Neurol. 2006; 10: 148-151.
26. Nangia S, Caraballo RH, Kang HC, Nordli DR, Scheffer IE. Is the ketogenic diet effective in specific epilepsy syndromes? Epilepsy Res 2012; 100: 252-257.
27. Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, Aberastury M, Silva W, Dulac O. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia 2010; 51: 2033-2037.
28. Villeneuve N, Pinton F, Bahi-Buisson N, Dulac O, Chiron C, Nabbout R. The ketogenic diet improves recently worsened focal epilepsy. Dev Med Child Neurol 2009;51: 276-281.
29. Rho JM, Stafstrom CE. The ketogenic diet: what has science taught us? Epilepsy Res 2012; 100: 210-217.
30. Keith HM. Factors inşuencing experimentally produced convulsions. Arch Neurol Psychiatr 1933; 29: 148-154.
31. Rho JM, Anderson GD, Donevan SD, White HS. Acetoacetate, acetone, and dibenzylamine (a contaminant in l-(+)-beta-hydroxybutyrate) exhibit direct anticonvulsant actions in vivo. Epilepsia 2002; 43: 358-361.
32. Dutton SB, Sawyer NT, Kalume F, Jumbo-Lucioni P, Borges K, Catterall WA, Escayg A. Protective effect of the ketogenic diet in Scn1a mutant mice . Epilepsia 2011; 52: 2050-2056.
33. Bough KJ, Yao SG, Eagles DA. Higher ketogenic diet ratios confer protection from seizures without neurotoxicity. Epilepsy Res 2000; 38: 15-25.
34. Appleton DB, DeVivo DC. An animal model for the ketogenic diet. Epilepsia 1974; 15: 211-227.
35. Hartman AL, Lyle M, Rogawski MA, Gasior M. Efficacy of the ketogenic diet in the 6-Hz seizure test. Epilepsia 2008; 49: 334-9.
36. Thavendiranathan P, Mendonca A, Dell C, Likhodii SS, Musa K, Iracleous C, Cunnane SC, Burnham WM. The MCT ketogenic diet: effects on animal seizure models. Exp Neurol 2000; 161: 696-703.

37. Daikhin Y, Yudkoff . Ketone bodies and brain glutamate and GABA metabolism. Dev Neurosci 1998; 20: 358-64.
38. Kumada T, Nishii R, Higashi T, Miyajima T, Oda N, Shimomura H, Saito K, Fujii T. Ketogenic diet may control seizures by increasing the binding potential of the benzodiazepine receptor: a speculation from the [11C] flumazenil-PET study. No To Hattatsu 2012; 44: 50-54.
39. Fraser DD, Whiting S, Andrew RD, Macdonald EA, Musa-Veloso K, Cunnane SC. Elevated polyunsaturated fatty acids in blood serum obtained from children on the ketogenic diet. Neurology 2003; 60: 1026-9.
40. Bromfield E, Dworetzky B, Hurwitz S, Eluri Z, Lane L, Replansky S, Mostofsky D. A randomized trial of polyunsaturated fatty acids for refractory epilepsy. Epilepsy Behav 2008; 12: 187-190.
41. Noh HS, Kim YS, Lee HP, Chung KM, Kim DW, Kang SS, Cho GJ, Choi WS. The protective effect of a ketogenic diet on kainic acid-induced hippocampal cell death in the male ICR mice. Epilepsy Res 2003; 53: 119-128.
42. Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. Prostaglandins Leukot Essent Fatty Acids 2004; 70: 309-319.
43. Ziegler DR, Ribeiro LC, Hagenn M, Siqueira IR, Araújo E, Torres IL, Gottfried C, Netto CA, Gonçalves CA. Ketogenic diet increases glutathione peroxidase activity in rat hippocampus. Neurochem Res 2003; 28: 1793-1797.
44. DeVivo DC, Leckie MP, Ferrendelli JS, McDougal DB Jr. Chronic ketosis and cerebral metabolism. Ann Neurol 1978; 3: 331-7.
45. Huang YZ, McNamara JO. Inhibiting glycolysis to reduce seizures: how it might work. Nat Neurosci 2006; 9: 1351-2.
46. Stafstrom CE, Ockuly JC, Murphree L, Valley MT, Roopra A, Sutula TP. Anticonvulsant and antiepileptic actions of 2-deoxy-D-glucose in epilepsy models. Ann Neurol 2009; 65: 435-47.
47. He XP, Kotloski R, Nef S, Luikart BW, Parada LF, McNamara JO. Conditional deletion of TrkB but not BDNF prevents epileptogenesis in the kindling model. Neuron 2004; 43: 31-42.
48. Xu L, Rensing N, Yang XF, Zhang HX, Thio LL, Rothman SM, Weisenfeld AE, Wong M, Yamada KA. Leptin inhibits 4-aminopyridine- and pentylenetetrazole-induced seizures and AMPAR-mediated synaptic transmission in rodents. J Clin Invest 2008; 118: 272-280.
49. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia 2004; 45: 1116-1123.
50. Furth SL, Casey JC, Pyzik PL, Neu AM, Docimo SG, Vining EP, Freeman JM, Fivush BA. Risk factors for urolithiasis in children on the ketogenic diet. Pediatr Nephrol 2000; 15: 125-8.
51. Kwiterovich PO Jr, Vining EP, Pyzik P, Skolasky R Jr, Freeman JM. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA 2003; 290: 912-20.
52. Vining EP, Pyzik P, McGrogan J, Hladky H, Anand A, Kriegler S, Freeman JM. Growth of children on the ketogenic diet . Dev Med Child Neurol 2002; 44: 796-802.
53. Nangia S, Caraballo RH, Kang HC, Nordli DR, Scheffer IE. I Is the ketogenic diet effective in specific epilepsy syndromes? Epilepsy Res 2012;100: 252-7.
54. Berry-Kravis E, Booth G, Sanchez AC, Woodbury-Kolb J. Carnitine levels and the ketogenic diet. Epilepsia 2001; 42: 1445-51.
55. Bergqvist AG, Schall JI, Stallings VA, Zemel BS. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. Am J Clin Nutr 2008; 88: 1678-84.
56. Sirikonda NS, Patten WD, Phillips JR, Mullett CJ. Ketogenic diet: rapid onset of selenium deficiency-induced cardiac decompensation. Pediatr Cardiol 2012; 33: 834-8.
57. Buse GJ, Riley KD, Dress CM, Neumaster TD. Patient with gemfibrozil-controlled hypertriglyceridemia that developed acute pancreatitis after starting ketogenic diet. Curr Surg 2004; 61: 224-6.
58. Bergqvist AG, Schall JI, Stallings VA. Vitamin D status in children with intractable epilepsy, and impact of the ketogenic diet. Epilepsia 2007; 48: 66-71.
59. McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff EH. Empiric use of oral Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. Pediatrics 2009; 124: 300-4.